

Claims

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1. A protein comprising a fibronectin type III domain having at least one randomized loop, said protein being characterized by its ability to bind to a compound that is not bound by the corresponding naturally-occurring fibronectin.

5 2. The protein of claim 1, wherein said fibronectin type III domain is a mammalian fibronectin type III domain.

3. The protein of claim 2, wherein said fibronectin type III domain is a human fibronectin type III domain.

10 4. The protein of claim 1, wherein said protein comprises the tenth module of said fibronectin type III domain ($^{10}\text{Fn3}$).

5. The protein of claim 4, wherein said compound binding is mediated by one $^{10}\text{Fn3}$ loop.

6. The protein of claim 4, wherein said compound binding is mediated by two $^{10}\text{Fn3}$ loops.

15 7. The protein of claim 4, wherein said compound binding is mediated by three $^{10}\text{Fn3}$ loops.

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8. The protein of claim 4, wherein the second loop of said $^{10}\text{Fn3}$ is

extended in length relative to the naturally-occurring module.

9. The protein of claim 4, wherein said $^{10}\text{Fn3}$ lacks an integrin-binding motif.

10. The protein of claim 9, wherein said integrin-binding motif is
5 replaced by an amino acid sequence comprising a basic amino acid-neutral amino acid-acidic amino acid motif.

11. The protein of claim 10, wherein said integrin-binding motif is replaced by an amino acid sequence comprising serine-glycine-glutamate.

12. The protein of claim 1, wherein said protein lacks disulfide bonds.

10 13. The protein of claim 1, wherein said protein is part of a fusion protein.

14. The protein of claim 13, wherein said fusion protein further comprises an immunoglobulin F_c domain.

15 15. The protein of claim 13, wherein said fusion protein further comprises a complement protein.

16. The protein of claim 13, wherein said fusion protein further comprises a toxin protein.

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17. The protein of claim 13, wherein said fusion protein further comprises an albumin protein.

18. The protein of claim 1, wherein said protein is covalently bound to a nucleic acid.

19. The protein of claim 18, wherein said nucleic acid encodes said protein.

20. The protein of claim 18, wherein said nucleic acid is RNA.

21. The protein of claim 1, wherein said protein is a multimer.

22. The protein of claim 1 or 9, wherein said protein is formulated in a 10 physiologically-acceptable carrier.

23. A nucleic acid encoding the protein of claim 1 or 4.

24. The nucleic acid of claim 23, wherein said nucleic acid is DNA.

25. The nucleic acid of claim 23, wherein said nucleic acid is RNA.

26. A method for generating a protein comprising a fibronectin type III 15 domain which is pharmaceutically acceptable to a mammal, said method comprising removing an integrin-binding domain from said fibronectin type III

domain.

27. The method of claim 26, wherein said integrin binding motif is replaced by an amino acid sequence comprising a basic amino acid-neutral amino acid-acidic amino acid motif.

5 28. The protein of claim 27, wherein said integrin-binding motif is replaced by an amino acid sequence comprising serine-glycine-glutamate.

29. The method of claim 26, wherein said at least one loop of said fibronectin type III domain is randomized.

10 30. The method of claim 26, wherein said protein comprises the tenth module of said fibronectin type III domain.

31. The protein of claim 26, wherein said protein is part of a fusion protein.

32. The protein of claim 31, wherein said fusion protein further comprises an immunoglobulin F_c domain.

15 33. The protein of claim 31, wherein said fusion protein further comprises a complement protein.

34. The protein of claim 31, wherein said fusion protein further

comprises a toxin protein.

35. The protein of claim 31, wherein said fusion protein further comprises an albumin protein.

36. The method of claim 26, wherein said mammal is a human.

5 37. A method for obtaining a protein which binds to a compound, said method comprising:

10 (a) contacting said compound with a candidate protein, said candidate protein comprising a fibronectin type III domain having at least one randomized loop, said contacting being carried out under conditions that allow compound-protein complex formation; and

15 (b) obtaining, from said complex, said protein which binds to said compound.

38. A method for obtaining a compound which binds to a protein, said protein comprising a fibronectin type III domain having at least one randomized loop, said method comprising:

20 (a) contacting said protein with a candidate compound, said contacting being carried out under conditions that allow compound-protein complex formation; and

(b) obtaining, from said complex, said compound which binds to said protein.

39. The method of claim 37, said method further comprising randomizing at least one loop of said fibronectin type III domain of said protein obtained in step (b) and repeating said steps (a) and (b) using said further randomized protein.

5 40. The method of claim 38, said method further comprising modifying said compound obtained in step (b) and repeating said steps (a) and (b) using said further modified compound.

41. The method of claim 37 or 38, wherein said compound is a protein.

10 42. The method of claim 37 or 38, wherein said fibronectin type III domain is a mammalian fibronectin type III domain.

43. The method of claim 42, wherein said fibronectin type III domain is a human fibronectin type III domain.

44. The method of claim 37 or 38, wherein said protein comprises the tenth module of said fibronectin type III domain ($^{10}\text{Fn3}$).

15 45. The method of claim 44, wherein said compound binding is mediated by one $^{10}\text{Fn3}$ loop.

46. The method of claim 44, wherein said compound binding is mediated by two $^{10}\text{Fn3}$ loops.

47. The method of claim 44, wherein said compound binding is mediated by three ¹⁰Fn3 loops.

48. The method of claim 44, wherein the second loop of said ¹⁰Fn3 is extended in length relative to the naturally-occurring module.

5 49. The method of claim 44, wherein said ¹⁰Fn3 lacks an integrin-binding motif.

50. The method of claim 37, wherein said compound is immobilized on a solid support.

10 51. The method of claim 38, wherein said protein is immobilized on a solid support.

52. The method of claim 50 or 51, wherein said solid support is a column or microchip.